SYMMETRICAL ADENOMATA OR NODULAR HYPERPLASIA OF THE SUPRA-RENAL GLANDS, AND EXTREME SCLEROSIS OF THE AORTA AND CORONARY ARTERIES.

BY

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Symmetrical adenomata or nodular hyperplasia of the suprarenal glands, and extreme sclerosis of the aorta and coronary arteries.

By F. Parkes Weber.

In 1903 O. Josué (1) succeeded in experimentally producing calcareous deposits and lesions resembling atheroma—that is to say, what the Germans generally term "arteriosclerosis"—in the aorta of rabbits by repeated intravenous injections of small doses of adrenalin.[1] His experiments have since then been repeated and in great part, or entirely, confirmed by a number

[1] In rabbits weighing over 2 kilogrammes Josué injected three drops of a 1 per mille solution of adrenalin every two days into the veins of the ear. Loeb and Githens (15) found that injections given at intervals of four days had more effect than the same number of injections of the same quantity given close together.

of separate observers (References, 3-15). The facility with which this "experimental atheroma" can be produced differs in different individuals. In some rabbits aortic lesions may be found after only two or three adrenalin injections.[1] The lesions, which may progress to actual aneurysmal formation, can be easily produced by intravenous injections, or, according to Külbs (12), by intra-tracheal injections, in old rabbits, but not in very young rabbits (Pic and Bonnamour, 5), nor in dogs (4), nor by subcutaneous injections, even in rabbits (Külbs, 12). According to Loeb and Githens (15) it seems probable that pregnant animals are less susceptible to the harmful action of adrenalin than are others. These observers found that adrenalin injections do not interfere with the course of pregnancy or delivery in rabbits, and have no effect on the development of the vascular system of the fœtus. The same observers found that renal lesions (produced by the administration of potassium chromate or by ligature of one ureter) and the consequent interference with the elimination of adrenalin did not appear to increase the susceptibility of rabbits to the vascular changes induced by adrenalin. According to the experiments of L. Lortat-Jacob and G. Sabaréanu (19) it appears that removal of the thyroid gland renders rabbits less susceptible and removal of the testicles makes them more susceptible to these harmful effects of adrenalin injections. Loeb and Githens (15), however, found that adrenalin atheroma occurred in spite of thyroidectomy. Diet seems to make some difference. According to A. von Koranyi (21) rabbits fed on turnips, etc., are less easily affected by experimental (adrenalin) atheroma than those fed on oats, and iodine in the form of subcutaneous injections of iodopin appeared to hinder the arterial changes in the animals experimented on (see also P. Boveri, 21).

I cannot here enter into the part played by excessive arterial blood-pressure in the production of "experimental atheroma." Lissauer (9) points out that the aortic lesions appear too early (in a few weeks)[2] to be explained on any mere blood-pressure

[1] The vascular lesions generally appear in a few weeks by Josué's method. In some animals the changes occur after only two to eight injections (1, 3, 11, 15). Braun (11) even says that experimental atheroma lesions may commence after only one or two injections.

[2] According to Josué (1), Rzentkowski (3), Braun (11), and Loeb and Githens (15), the aortic lesions may appear in some rabbits after only one or two (Braun) to eight adrenalin injections.

hypothesis. Loeb and Githens (15) found that intravenous injections of pyrocatechin, which have been shown by Dakin (16) to cause marked rise in blood-pressure, were quite incapable of producing any vascular lesions in rabbits comparable to those produced by adrenalin. Sturli (10) from his experiments with methylamin-acetopyrocatechin and adrenalin, and Mironescu (22) from his trials with euphthalmin and adrenalin, conclude that experimental atheroma in rabbits is due to a direct toxic action of the adrenalin on the arterial wall, though the latter observer admits that changes in blood-pressure, due to the adrenalin, may favour the production of the arterial lesions in question. Josué (quoted by Loeb and Githens, 15) found that nicotin, though it causes a rise of blood-pressure, has no effect on the structure of the vessel walls. L. Braun (11) found that the simultaneous injection of amyl nitrite, though it prevented rise of blood-pressure, did not prevent the occurrence of the adrenalin lesions, but von Koranyi and also P. Boveri (21), as already stated, found that iodine hindered their appearance.[1]

It is interesting to note that, as R. M. Pearce (14) and B. Fischer (4) have shown, Josué's method of adrenalin injections produces myocardial in addition to arterial disease, and that the myocardial changes thus produced are by no means all secondary to stenosis of the coronary arteries. In about half the number of animals experimented on in which the heart changes were examined severe myocardial lesions were found unaccompanied by arterial disease (Pearce, 14). The pulmonary artery seems never to be affected (4 and 12).

Many of the observers have denied the identity of Josué's "experimental atheroma" with the atheroma of the aorta and large arteries which is frequently found at *post-mortem* examinations on human beings. W. Erb, junior (16), and some others (7, 8, 9, 14) of those who have repeated Josué's experiments, believe that artificial atheroma produced by adenalin injections in animals is not analogous to human arterial atheroma, but regard it as more nearly resembling the primary calcification of

[1] For a discussion and summary on the physiological action of adrenalin on unstriped muscular tissue see T. R. Elliott, "The Action of Adrenalin," 'Journal of Physiology,' Cambridge, 1905, vol. xxxii, pp. 401 to 467. In regard to the connection between experimental atheroma and changes in blood-pressure see also H. Batty Shaw, 'Lancet,' 1906, vol. i, p. 1459.

the middle coat, which has been especially investigated by J. G. Mönckeberg (25), sometimes met with in the arteries of the arms and legs in man. The syphilitic aortitis which leads to the development of aneurysms in man is now believed by many to be a proliferative or plastic mesaortitis, the "mesaortitis productiva" of H. Chiari (24). According to Albrecht (17) the adrenalin lesions by their localisation and their tendency to lead to aneurysmal dilatations resemble the results of this syphilitic aortitis, but differ from them by the presence of primary necrotic changes in the media and by the ready disappearance of evidence of any original inflammation. On the other hand, as the suprarenal capsules appear to be especially invaded by the *Spirochæta pallida* in congenital syphilis, it has been suggested (Josué, 18) that changes originally set up by the spirochætæ in these glands may constitute a connecting link serving to explain the frequency of ordinary aortic atheroma in syphilitics.[1]

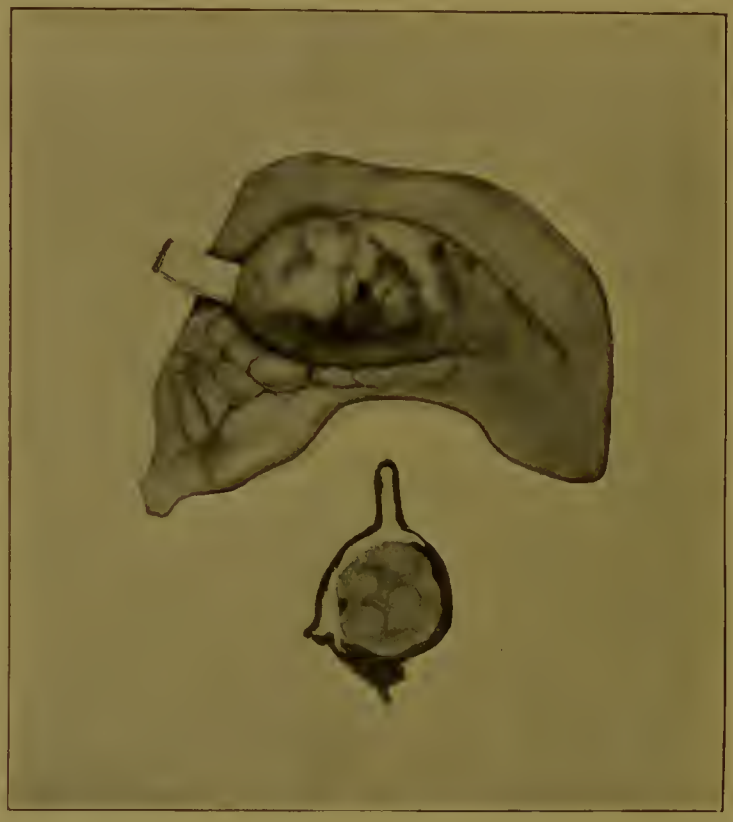
Josué (2), and Widal and Boidin (23), have drawn attention to the association of generalised atheroma with hypertrophy and adenomata of the suprarenal capsules, and it is to a case of this nature to which I now wish to draw attention.

The patient, a German, Michael F—, aged 59 years, weighing 76 kilogrammes, was admitted to the German Hospital on March 15th, 1906. Very little past history was obtained. For several months he had been suffering from shortness of breath and cough, with slight expectoration. For some weeks his legs had been swollen. Examination of the thorax showed the presence of pulmonary emphysema. Dry sounds were heard all over the lungs, and there were occasional crepitations over the lower lobes. The heart was evidently abnormally covered by lung-tissue; the apex beat could not be felt, and the sounds were faint; no murmur could be detected. Pulse 88, regular; the radial artery felt rather too hard; the brachial blood-pressure as measured by the Riva-Rocci apparatus with the broad band, was 130 mm. mercury. The liver could be felt about three fingers' breadths below the costal margin. The spleen seemed not to be enlarged.

[1] Similarly in regard to the connection between chronic saturnism and arterial disease, it may be noted that Gouget (14) has experimentally produced hypertrophy of the suprarenal capsules as well as aortic atheroma in a guinea-pig by the administration of carbonate of lead.

There was a scar in the abdomen from an old laparotomy wound (an operation had been performed six years previously) with a ventral hernia in the scar. Both legs were œdematous and the arms slightly so. The urine was of specific gravity 1·025, free from sugar, but containing a little albumen (under $\frac{1}{2}$ per mille by Esbach's tube); a few hyaline casts were seen

Fig. 35.



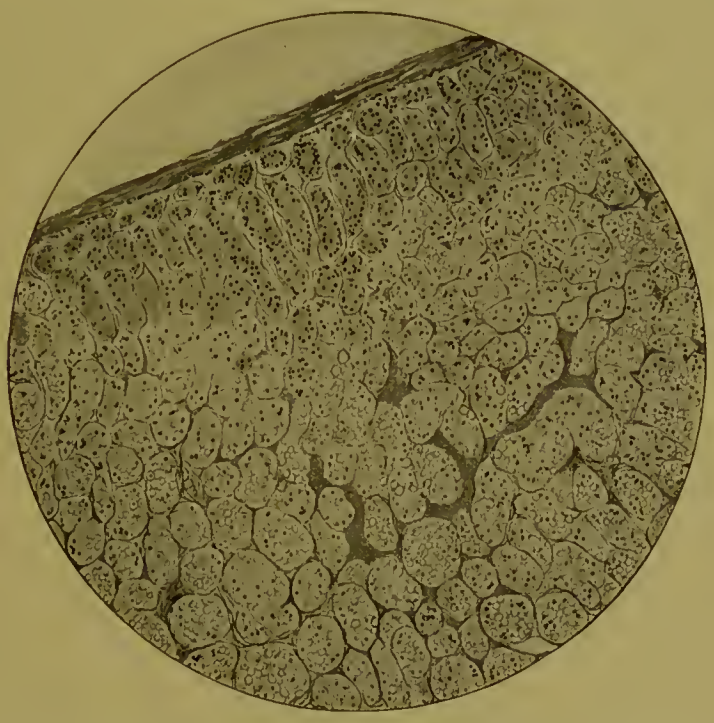
Showing one of the adrenals with the adenoma projecting from the surface, and a vertical section of the same. In the latter the cortical substance is represented darker than the medullary.

in the sediment obtained by the centrifugal machine. There was no fever. The patient died suddenly three days after admission.

At the necropsy (on the following day) the *heart* showed moderate hypertrophy and much dilatation, chiefly of the left ventricle. Both coronary arteries were greatly sclerosed; at parts they were quite rigid and their lumens greatly narrowed, if not completely blocked. Portions of the myocardium, notably

portions close to the internal ventricular surface, had obviously undergone degenerative changes, probably secondary to the coronary artery disease. There was some *ante-mortem* thrombus at the apex of one of the ventricles. The aorta (especially the abdominal portion) showed extreme sclerotic changes with deposition of calcareous plates. In our examination of the abdomen no explanation of the old laparotomy was forthcoming. The liver, somewhat enlarged, was "nutmeggy" from chronic passive

FIG. 36.



A microscopic section showing part of the tumour of the cortex and the large vacuolated fatty cells of which it mainly consists. (Zeiss A.)

congestion. The kidneys were of good size, but there was naked-eye evidence of a certain amount of chronic interstitial nephritis. The spleen, slightly too large, contained an old infarct.

The suprarenal glands together weighed about 19 grammes. Imbedded in the cortical substance and projecting on the surface of each gland there was an oval-shaped nodule, measuring about 25 × 15 × 15 mm.—that is, about as large as an ordinary Muscat grape. A microscopic section (from the right capsule) shows one of these nodules to have the typical structure of an ordinary suprarenal adenoma—*i. e.* of a hypertrophic

nodule of the cortical substance, with the customary fatty degeneration of the cells. A section of one of the nodules especially stained with Sudan III (for which I am indebted to the kindness of Mr. Shattock) shows that the cells are loaded with fat-globules. The suprarenal medullary substance seems not to be affected except by pressure due to the cortical growth. One of the suprarenal capsules and part of the atheromatous aorta from the case are preserved in the Museum of the Royal College of Surgeons.

By microscopical examination it was found that the degenerative and calcareous change in the aorta was by no means confined to the inner coat, for the middle (muscular) coat was extensively involved. Even in relatively little affected spots of the wall of the aorta the unstriped muscle of the media appeared hazy and degenerating, and showed a deposit of very fine granules (the earliest stage of calcification). Both in the middle coat and the outer coat (tunica adventitia) there were likewise scattered spots of small cell infiltration. The question arises whether the aortic disease in the present case may not be regarded as specially resembling Chiari's "mesaortitis productiva," and the "experimental" mesaortitis (or rather "mesarteriocerosis" of the aorta) produced in rabbits by intravenous adrenalin injections.

I take this opportunity of thanking Dr. Sehuh, house physician at the German Hospital, for preparing sections of the aorta and suprarenal capsule.

The present case is of some interest as it fits in with Josué's views (2) of a causal connection between suprarenal adenomata (or hyperplasia of the cortical gland substance) on the one hand and aortic and generalised atheroma on the other. Of course, the association may be a chance one, but it must be remembered that neither the symmetrical adenomata of the suprarenal glands nor (even in old persons) the extreme changes in the aorta and coronary arteries are common conditions.

Whereas in adults there is perhaps some causal connection between atheroma-like aortic lesions and suprarenal hypertrophy, there seems in children to be certainly a causal connection between the presence of suprarenal hypertrophy or hypernephromata (that is to say, tumours derived from the suprarenal cortical gland-cells) on the one hand and precocious general and

sexual development on the other. An excellent summary on the relation of the suprarenal glands to the sexual organs has been recently given by W. Bulloch and J. H. Sequeira at the Pathological Society of London (26). It is possible, then, that overgrowth of the suprarenal glandular tissue (and excess of the suprarenal secretion) may be connected with different general conditions according to age—*i. e.* in childhood, with precocious development and after middle life with arterial atheroma. One might point out a possible analogy in the case of the hypophysis cerebri. Overgrowth of pituitary gland during the growing period of life may be connected with gigantism, and after the normal period of growth has ceased with acromegaly.

In regard to the action of adrenalin injections in animals it may be remembered that Pic and Bonnamour (5) failed to produce "experimental atheroma" by Josué's method in rabbits that were still very young. It would therefore be very interesting to know whether in young (still growing) rabbits or other animals repeated but relatively very minute injections of adrenalin could produce precocious general and sexual development in place of the aortic changes it produces in old rabbits.

Addendum.

Since writing the above account I have had the advantage of hearing some friendly criticism on it. Mr. S. G. Shattock in particular points out that "adrenalin" is furnished from the medulla, but not from the cortical substance of the suprarenal glands, and that in the present case, as far as the microscopic examination went, no decided changes were found in the medullary substance, the adenomata being undoubtedly of cortical origin; it has occurred to me, however, that the presence of suprarenal adenomata may possibly act as a mechanical irritant, both producing hyperæmia of the whole organ and stimulating the functional activity of the medullary cells.

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